await a transient ischaemic attack[w2] or, even worse, an acute infarction for which an urgent endarterectomy is required[w3] is therefore not good advice. However, others take a contrary view, perhaps because of a lack of facilities, excessive competition rates owing to poor selection of candidates, or inept surgery. Moreover, an attitudinal bias may also exist regarding prevention among doctors who have been trained to intervene only if malfunction of an organ becomes symptomatic.

The degree of stenosis is measured by different methods, and for most specialists 60% stenosis is the cut-off point for selecting patients for endarterectomy. This has led to an erroneous concept that a minimum of 60% stenosis of the internal carotid lumen is the essential criterion.[3] However, other key indicators are turbulent flow caused by stenosis, sludge due to eddy currents, particulate microemboli, and wall abnormalities that are resistant to medical management.[4]

Screening for asymptomatic carotid atherosclerosis by using auscultation for bruits and duplex ultrasonography is feasible and is currently the best way of identifying preclinical atherosclerosis.[5] Patients identified by preliminary screening to determine flow dynamics, arterial wall characteristics including stenosis and ulceration, and microemboli, to identify those for whom medical management is needed and to assess the effect of medical remediation.[6 w4] If medical intervention fails, ACST has proved once and for all that carotid endarterectomy can be worth the risk if surgical and anaesthetic skills are such that operative complications are rare.[7]

International collaborative studies such as these require a huge investment of time, skill, and money and are an endorsement of evidence based medicine first promulgated by Austin Bradford Hill and Sir Richard Doll.[8 w5] For the field of stroke, the baseline from which they evolved were the autopsy findings of Miller Fisher,[w6] followed by the landmark report by Eastcott, Pickering, and Robb at St Mary's Hospital in London.[9] Carotid endarterectomy has now come full circle, having been validated by Halliday, Thomas, and colleagues of the same institution.[2] Their multinational effort continues the search for better methods by which to identify people with atherosclerosis who should be considered for medical and surgical intervention.

So far, differentiating symptomatic from asymptomatic stenosis of the carotid artery has traditionally been the way to decide on treatment. But this requires a doctor skilled in neurology to make the judgment. Moreover, the occurrence of transient ischaemic attacks is not a satisfactory means of categorisation because they are very seldom witnessed, cannot be assessed objectively, are confounded by many other transitory phenomena, and may occur during sleep when they cause no recognisable phenomena or in parts of the brain that do not produce symptoms or signs.[10 11] Moreover, 3-10% of people older than 65 have asymptomatic infarcts visible on brain imaging.[12]

Depending on transient ischaemic attacks for categorising patients is therefore unacceptable as the sole criterion for choosing treatment, and preclinical stenosis and unrecognised transient ischaemic attacks need to be identified by screening.

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Forensic science in the dock

Postmortem measurements of drug concentration in blood have little meaning

Investigations into the circumstances surrounding the death of David Kelly have led to the exchange of acrimonious views including allegations of conspiracy and murder. David Kelly, a government scientist and weapons expert, committed suicide by cutting his wrist and taking painkillers after he was identified in newspapers as the man the UK government believed was the source for a BBC report on Iraq. Impetus for the debate stems mainly from conflicting views about the cause of death, including issues that relate to postmortem toxicology results and their interpretation. Controversy occurs from the mistaken notion that postmortem laboratory measurements, taken in isolation, can be interpreted effectively.

The current controversy illustrates some universally held, but mistaken, notions about the process of death investigation in the United Kingdom and elsewhere. Many assume that forensic pathology is as evidence based as other branches of medicine. This assumption is not accurate.

In the course of caring for living patients, doctors who interpret hospital laboratory tests know, or can quickly find out, the "normal" value for any particular drug. But most doctors (as well as the general public) would be surprised to learn that there are few if any

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"normals" in postmortem toxicology. Non-circulating blood after death is not the same thing as circulating blood before death, and evidence that the concepts of normal or therapeutic drug concentrations can be applied to blood from dead bodies is severely lacking.

Even in living bodies, interpretation of a single blood concentration measurement is impossible without considering route of administration, number of doses taken, and the amount of drug actually in the body. Such information is almost never available to investigators, making it impossible to determine the cause of death solely by comparing a single postmortem drug concentration measurement with a range of published values, originally derived from measurements made in living people. With chronic use, tolerance occurs, and tolerance cannot be measured or estimated after death. Healthy patients enrolled in methadone maintenance programmes, for example, may have blood methadone concentrations in excess of other, non-tolerant methadone users examined on the autopsy table.[1] Similarly, we have long known that blood sampled from the heart of a dead person who had been on long term digoxin treatment may contain a seemingly toxic concentration of digoxin when, in fact, the actual blood concentration immediately before death was the appropriate non-toxic therapeutic concentration.[2]

Even if it could be shown that blood concentrations after death were the same as concentrations at the time of death, which blood sample should be used? Drug concentrations are likely to have changed after death.[3] For many drugs, including those found in David Kelly, concentrations may increase by as much as 10-fold.[4] Furthermore, drug concentrations in blood samples from cadavers are site dependent, higher in some locations and lower in others.[5] Should the site yielding the lowest or highest result be used? Or should an average value for three sites be used? Nobody knows because the process has never been studied systematically.

If the blood concentration at the time of death cannot be known with certainty, then how is it possible to extrapolate the time and amount of drug ingested before death? The simple answer is that such extrapolations are prone to considerable error and generally should be viewed as unreliable and not evidence based.[6] Despite these limitations, such calculations are frequently and wrongly produced during court proceedings, even though the problems we outline have been widely known for many years.

Postmortem measurements of drug concentration in blood have scant meaning except in the context of medical history, the sequence and circumstances surrounding death, and necropsy findings. The paucity of evidence based science, coupled with the pretence that such science exists in regard to postmortem toxicology, leads to the abuse of process, almost certainly to the miscarriage of justice, and possibly even to false perceptions of conspiracy and cover up.

We have written this editorial partly because of the Kelly matter, where the central issue concerned the interpretation of the toxicology results. Death investigation and forensic pathology are also not immune to misinterpretation. Poor or inadequate death investigation and incomplete or misinterpreted forensic pathology studies may also result in wrong conclusions. All aspects of the medicolegal death investigation triad—investigation (history), pathology, and laboratory results—are essential and must be evaluated in context with one another. We have formed an ad hoc group to address this issue. A detailed analysis of the problem with suggestions for reform is in preparation.

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Compulsory registration of clinical trials

Will be a requirement before submission to the BMJ from July 2005

"The case for registering all clinical trials—first advanced a decade ago[1]—is now unanswerable."[2] Editors of the *BMJ* and the *Lancet* made this statement in 1999. Five years of industry resistance, government impotence, and public confusion followed. Medical journals persisted with noble intentions and wise words but were themselves in part resistant, impotent, and confused about how to enforce registration. Some journals, including the *BMJ*, tried an amnesty for unpublished trials, with little success.[3] The *BMJ* also considered asking for compulsory registration, but it seemed to us that trial registries were too diverse, disorganised, and easily disregarded to insist on registration before submission. Nor did we

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